UNITED STATES DISTRICT COURT
WESTERN DISTRICT OF LOUISIANA
LAFAYETTE DIVISION

IN RE: ACTOS® (PIOGLITAZONE) PRODUCTS LIABILITY LITIGATION

MDL No. 6:11-md-2299

JUDGE DOHERTY

MAGISTRATE JUDGE HANNA

This Document Applies To:
Allen, et. al. v. Takeda Pharmaceuticals North America, Inc., et al.
(Case No. 12-cv-00064)

MEMORANDUM RULING:
SEBASTIAN SCHNEEWEISS, M.D., S.M., S.C.D., F.A.C.E., F.C.P., F.I.S.P.E.

This multidistrict litigation arises from product liability claims against the manufacturer and marketer of Actos® and other drugs containing pioglitazone. Pending before this Court is the Defendants' Motion to Exclude Testimony of Plaintiffs' Expert, Sebastian Schneeweiss, M.D., S.M., S.C.D., F.A.C.E., F.C.P., F.I.S.P.E.[1] For the reasons, the Defendants' Motion will be denied.

EVIDENCE AT ISSUE

Dr. Schneeweiss, a Professor of Medicine at Harvard Medical School, Professor of Epidemiology at Harvard School of Public Health, and Vice-Chief of the Division of Pharmacoepidemiology in the Department of Medicine at Brigham & Women's Hospital, has submitted a 52-page report, together with various appendices, reference lists, etc. presenting the following opinions, together with the analysis and information upon which the following opinions are based:

[1] Rec. Doc. 3464. This motion has been urged on behalf of all named defendants in this matter. The Memorandum in Support of Defendants' Motion to Exclude Testimony of Plaintiffs' Expert Sebastian Schneeweiss, M.D. is found at Rec. Doc. 3464-1 ["Memorandum"]; the Plaintiffs' Memorandum of Law in Opposition to Defendants' Motion to Exclude Testimony of Plaintiffs' Expert Sebastian Schneeweiss, M.D. is found at Rec. Doc. 3606 ["Opposition"]; and the Defendants' Reply in Support of Defendants' Motion to Exclude Testimony of Plaintiffs' Expert Sebastian Schneeweiss, M.D. is found at Rec. Doc. 3670 ["Reply"]. For these purposes only, the Court will make no distinction between and among Defendants as, for these purposes, there is no legal distinction.

- Pioglitazone (Actos®) is an independent risk factor for bladder cancer in patients with diabetes and is itself a cause of bladder cancer in exposed individuals;

- Pioglitazone (Actos®) confers a statistically significant increased risk for the development of bladder cancer in exposed individuals that ranges from 1.38 for ever use to a near-tripling of the risk as seen in the randomized control trials;

- The causal relationship between pioglitazone (Actos®) and bladder cancer exhibits a consistent dose-response relationship that further supports the causal relationship between this drug and bladder cancer;

- Smoking status, race, duration of diabetes, recurrent urinary tract infections, obesity, occupational exposure are highly unlikely to be confounders in studies of the development of bladder cancer in individuals exposed to pioglitazone (Actos®); and

- There is substantial evidence to support an increased risk of bladder cancer even with short-term use of pioglitazone (Actos®), *i.e.*, use that is less than one year of duration.[2]

The Defendants do not challenge Dr. Schneeweiss' qualifications, nor the relevance of his opinions. The Defendants' sole challenge is to the reliability of Dr. Schneeweiss' opinions.

LAW AND ANALYSIS

I. APPLICABLE LAW

While state law governs the Plaintiffs' claims in this matter, the Federal Rules of Evidence control the admission of expert testimony.[3] Under the Federal Rules of Evidence, "relevant" evidence is admissible, while irrelevant evidence not admissible.[4] Evidence is "relevant" if it has any tendency to make a fact more or less probable than it would be without the evidence, and the fact being proven or disproven is of consequence in determining the action.[5] The party seeking to have expert opinion testimony admitted into evidence bears the

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[2] Dr. Schneeweiss' Report, at 52. Dr. Schneeweiss' report will be referred to herein as "the Schneeweiss Report." It has been submitted as the Defendants' Omnibus Exhibit C11 and the Plaintiffs' Exhibit A.

[3] Huss v. Gayden, 571 F.3d 442, 452 (5th Cir. 2009), *citing* Mathis v. Exxon Corp., 302 F.3d 448, 459 (5th Cir. 2002).

[4] F.R.E. 402.

[5] F.R.E. 401.

burden of demonstrating, by a preponderance of the evidence, that the expert's findings and conclusions are based on the scientific method and, therefore, are reliable.[6]

The Federal Rules of Evidence require that a judge, faced with a proffer of expert scientific testimony, must begin by determining, pursuant to Rule 104(a), whether the expert is proposing to (i) testify to scientific knowledge (ii) that will assist the trier of fact to understand or determine fact in issue.[7] This will require a preliminary assessment of whether the reasoning or methodology underlying the testimony is scientifically valid and of whether that reasoning or methodology properly can be applied to the facts in issue.[8] This requirement is found in Rule 702 of the Federal Rules of Evidence, which reads as follows in its entirety:

> A witness who is qualified as an expert by knowledge, skill, experience, training, or education may testify in the form of an opinion or otherwise if:
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> (a) the expert's scientific, technical, or other specialized knowledge will help the trier of fact to understand the evidence or to determine a fact in issue;
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> (b) the testimony is based on sufficient facts or data;
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> (c) the testimony is the product of reliable principles and methods; and
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> (d) the expert has reliably applied the principles and methods to the facts of the case.

In the United States Supreme Court's landmark decision in Daubert v. Merrell Dow Pharmaceuticals, Inc., the Court acknowledged the existence of a federal court's gatekeeping role with regard to expert scientific opinion testimony, characterizing that role as one ensuring

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[6] Moore v. Ashland Chemical, Inc., 151 F.3d 269, 276 (5th Cir. 1998) (*en banc*).

[7] Daubert v. Merrell Dow Pharmaceuticals, Inc., 509 U.S. 579, 592, 113 S.Ct. 2786, 2796, 125 L.Ed.2d 469 (1993).

[8] Id., 509 U.S. at 592-93; Moore, 151 F.3d at 276.

that such evidence meet the requirements of both reliability and relevance.[9] "Reliability" as discussed in Daubert refers to *evidentiary* reliability, *i.e.*, trustworthiness, rather than *scientific* reliability, which asks whether application of the principle produces consistent results, a distinction often blurred by Defendants' arguments. In a case involving scientific evidence, evidentiary reliability is based upon scientific validity, which asks whether the principle supports what it purports to show.[10]

The objective of this requirement is to make sure that an expert, whether basing testimony upon professional studies or personal experience, employs in the courtroom the same level of intellectual rigor that characterizes the practice of an expert in the relevant field.[11] The Supreme Court identified several non-exclusive factors a court should consider in determining whether proffered scientific opinion testimony is sufficiently reliable to permit admission into the record.[12] Those factors are:

- whether the expert's theory can be or has been tested;
- whether the theory has been subject to peer review and publication;
- the known or potential rate of error of a technique or theory when applied;
- the existence and maintenance of standards and controls; and
- the degree to which the technique or theory has been generally accepted in the scientific community.[13]

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[9] Moore, 151 F.3d at 275.

[10] Daubert, 509 U.S. at 590 n.9.

[11] Kumho Tire Company, Ltd. v. Carmichael, 526 U.S. 137, 152, 199 S.Ct. 1176, 143 L.Ed.2d 238 (1999). *See also* Brown v. Illinois Central Railroad Co., 705 F.3d 531, 535 (5th Cir. 2013).

[12] *See* discussion, 509 U.S. at 594-595.

[13] Moore, 151 F.3d at 275.

Several years later, the Supreme Court clarified when it held the gatekeeping role applied to all types of expert opinion testimony, not just scientific evidence, and revisited the reliability analysis.[14] Moreover, the Supreme Court reiterated that a court must have considerable leeway in deciding, in a particular case, how to go about determining whether particular expert testimony is reliable.[15] Therefore, the test of reliability is flexible and there is no necessary or exclusive list of factors that must exist in order for a particular opinion to be admissible.[16]

> Daubert makes clear that the factors it mentions do not constitute a definitive checklist or test. Daubert adds that the gatekeeping inquiry must be tied to the facts of a particular case. We agree with the Solicitor General that the facts identified in Daubert may or may not be pertinent in assessing reliability, depending on the nature of the issue, the expert's particular expertise, and the subject of his testimony. The conclusion, in our view, is that we can neither rule out, nor rule in, for all cases and for all time the applicability of the factors mentioned in Daubert, nor can we now do so for subsets of cases categorized by category of expert or by kind of evidence. Too much depends upon the particular circumstances of the particular case at issue.[17]

In the Fifth Circuit, "[t]o determine whether proffered testimony is reliable, the trial court must make 'a preliminary assessment of whether the reasoning or methodology underlying the testimony is . . . valid and of whether that reasoning or methodology properly can be applied to the facts in issue.'"[18] Further, "[t]o establish reliability under Daubert, an expert bears the burden of furnishing 'some objective, independent validation of [his] methodology.'"[19] In doing

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[14] Kumho Tire, 526 U.S. at 141-142.

[15] Id. at 152.

[16] Id. at 141-142, 149.

[17] Id. at 150 (citations and quotation marks omitted).

[18] Brown v. Illinois Central Railroad Co., 705 F.3d 531, 535 (5th Cir. 2013) (*quoting* Daubert, 509 U.S. at 592–93).

[19] Brown, 705 F.3d at 536 (*quoting* Moore, 151 F.3d at 276).

so, "[t]he expert's assurances that he has utilized generally accepted [principles] is insufficient."[20]

In Brown the Fifth Circuit held that the trial court did not abuse its discretion where an expert testified that offered opinions were reliable merely upon and because of "education and experience" and did not engage in or rely upon a credible methodology, particularly in the face of evidence in opposition to those opinions. Standing alone then, it is insufficient for an expert to base his or her opinion on education and experience alone, especially in the face of evidence to the contrary.

The Defendants' Motion does not challenge the proffered opinion testimony, nor the qualifications of Dr. Schneeweiss.

II. ANALYSIS

Plaintiffs bear the ultimate burden on this issue, thus, this Court will first look to Plaintiffs' *prima facie* showing. The task for this Court within this Motion, as the gatekeeper, is to determine whether the Plaintiffs' experts will have the necessary qualifications, employed a required process, methodology, rely upon sufficiently sound scientific evidence and comport with the inquiry and factors identified in Daubert, within their respective areas of expertise so as to be allowed to pass the gatekeeper inquiry. The specific analysis of this issue will begin with consideration of the Plaintiffs' evidence in support of their *prima facie* case, and then proceed to consideration of the Defendants' specific challenges.

A. Dr. Schneeweiss' Report, Opinions, and Supporting Evidence

Dr. Schneeweiss has provided a report in this matter. The body of the Schneeweiss Report is 52 pages in length, with an attached list of the 127 references upon which Dr. Schneeweiss relied in developing his opinions, an appendix discussing biases that have the

[20] Id. (*quoting* Moore, 151 F.3d at 276).

potential to lead to erroneous conclusions about causal associations , an appendix explaining his grading system for evaluating epidemiological evidence, an appendix describing the statistical methods he used, and a list of the case materials he reviewed in developing his opinions and producing his report.

The Schneeweiss Report contains:

- a description of his qualifications and credentials;[21]
- a description of his methodology;[22]
- a description of the process by which he reached his epidemiological conclusions in this matter;[23]
- an extensive discussion of the pitfalls and difficulties associated with using non-randomized studies of pioglitazone;[24]
- a discussion of the other risk factors he considered;[25]
- an extensive discussion of many epidemiological studies, including randomized controlled studies (two, both conducted by Takeda), non-randomized studies (divided into studies of one study with higher evidentiary value, three studies with moderate evidentiary value, and 13 studies with low evidentiary value);[26]
- a clear discussion of the Bradford Hill criteria[27] for determining causation and their application to the facts and data in this case;[28] and

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[21] The Schneeweiss Report, at 4-5.

[22] Id., at 7-8, Appendices I-III.

[23] Id., at 7-8 (discussion of Bradford Hill criteria).

[24] Id., at 9-19.

[25] Id., at 12-13.

[26] The Schneeweiss Report, at 21-49.

[27] The Bradford Hill criteria are often used within the scientific community to assess a possible causal association. The Bradford Hill criteria are: (1) a temporal relationship; (2) strength of the causal association; (3) a dose-response relationship; (4) replication of the findings; (5) biological plausibility (coherence with existing knowledge); (6) consideration of alternative explanations; (7) cessation of exposure; (8) specificity of the association; and (9) consistency with other knowledge. REFERENCE MANUAL ON SCIENTIFIC EVIDENCE, at 600 (3d ed. 2011). Because there is no formula or algorithm that can be used to assess whether a causal influence is appropriate based on these guidelines, one or more factors may be absent or present even when a true causal relationship exists. Id. (citations omitted).

- a list of the opinions he has reached in this matter.[29]

This Court has conducted an exhaustive review of the briefs, the exhibits submitted in support of both parties' arguments, and all studies and reports, including those specifically of Dr. Schneeweiss that are under challenge with the instant motion. This Court finds, as a threshold matter, that Dr. Schneeweiss is qualified to develop the opinions he has reached in this case, that as a threshold matter, he relied on standard and accepted scientific method(s) of reviewing otherwise reliable scientific evidence, in formulating those opinions and again, as a threshold matter, the studies, publications and data which he relied upon were sufficiently reliable as to overcome Defendants' threshold challenge. This Court has considered the five illustrative factors noted below and identified in Daubert and concluded that they either weigh in favor of the admissibility of Dr. Schneeweiss' opinions and foundational underpinnings or, alternatively, do not weigh in favor of the exclusion of the challenged opinions and foundational underpinnings.

B. Rule 702/Daubert Factors

After full review of all argument, evidence and supporting documentation, this Court finds the five factors identified in Daubert, either weigh in favor of the admissibility of Dr. Schneeweiss' causation opinions or do not weigh in favor of their exclusion of the challenged evidence.

- ***Testability***. Dr. Schneeweiss' method(s) of review of reliable scientific evidence have been employed, studied, tested, and published in peer review literature, as have the studies on which he relies. As a threshold matter, the testability of the foundational underpinnings of Dr. Schneeweiss' theory support a finding of admissibility. The fact that Dr. Schneeweiss has not engaged in independent testing of pioglitazone, himself, but relies on published studies, is not fatal under the circumstances in this case because he has used an acceptable methodology of review

[28] The Schneeweiss Report, at 50-51.

[29] Id., at 52.

and the underlying foundational underpinnings of that review, themselves, have been tested.

- ***Peer Review.*** Dr. Schneeweiss has cited a great many peer-reviewed publications that provide scientific support for his opinions. While it does not appear that Dr. Schneeweiss' specific opinions in this case have been subjected to peer review, this Court finds the *underlying studies* relied upon, incorporated, and used as foundational support for his conclusions, are and have been sufficiently subject to peer review and are accepted within the relevant scientific community. The absence of peer review for Dr. Schneeweiss' opinions, themselves, in and of itself, does not invalidate Dr. Schneeweiss' opinion when the otherwise accepted methodology of review has been employed to extrapolate information from peer-review publications. Dr. Schneeweiss' heavy reliance on identified peer-reviewed publications, studies, and information – together with his discussion and consideration of those studies he finds unpersuasive – as a threshold matter lend strong support for the argument in favor of admissibility of his opinion and foundational support for his conclusions.

- ***Rate of Error.*** Each underlying study relied upon by Dr. Schneeweiss has a rate of error attached to the theory or technique used and is readily available for review and cross examination. The absence of a rate of error as to his specific opinions should not be fatal in the face of such error rates as to each underlying study.

- ***Standards and Controls.*** Dr. Schneeweiss is a qualified epidemiologist who has conducted his investigation and review, and developed his opinions, in this matter, in compliance with the standards and controls under which he normally operates in his professional life. This Court finds that those standards and controls lend strong support for the argument of/for reliability of Dr. Schneeweiss' opinions, as a threshold matter.

- ***General Acceptance.*** Dr. Schneeweiss' report provides ample evidence that his epidemiological methodology is generally-accepted in the scientific community and that his investigation, while it hasn't been conducted or replicated by any third party, is fully consistent with those generally-accepted principles. Dr. Schneeweiss' review process employed, conclusions reached, and opinions posited have been guided by scientifically-accepted processes employed within the accepted scientific method, and stand upon a foundation of independent peer-reviewed studies and articles. Consequently, this factor argues for allowing presentation of Dr. Schneeweiss' opinions for evaluation by the trier of fact.

This Court, also, notes, that unlike in Brown, here, the opinions Dr. Schneeweiss offers are not based merely on his "education and expertise." Dr. Schneeweiss relies on multiple studies, and publications, and extensive data, and utilizes the Bradford Hill criteria in conducting his epidemiological investigation and reaching his causation opinions. Indeed, Dr. Schneeweiss applies each of the nine (9) Bradford Hill criteria – criteria which are both reliable and credible

and under which he formulates his general causation opinion. Had Dr. Schneeweiss merely relied on this "education and expertise" as did the expert in Brown, Defendants' argument would be more persuasive, however, that is not the case. This Court finds that Dr. Schneeweiss' opinions do not fail the threshold test of Brown, that the Plaintiffs have met their *prima facie* burden of demonstrating, as a threshold matter, that Dr. Schneeweiss' opinions are admissible.

C. The Defendants' Challenges

As a preliminary and threshold matter, this Court notes that Dr. Schneeweiss' opinions and analysis are presented to support the Plaintiffs' theory of general causation, specifically, that there is a potential for pioglitazone to either cause or promote the development of bladder cancer and that it can do so within the first year of exposure. The gravamen of the dispute between the Plaintiffs and the Defendants as to Dr. Schneeweiss' investigation, analysis, opinions, and conclusions – together with the role that those opinions and conclusions play in the Plaintiffs' overall theory of general causation – has been addressed to some degree in this Court's Memorandum Ruling: Development of Bladder Cancer Within One Year of Exposure Rec. Doc. 3771] which is incorporated and adopted herein. Moreover, many of the challenges to Dr. Schneeweiss' report and opinions are similar, if not identical, to challenges asserted by Defendants in response to Dr. Delacroix's report and opinions. This Court will address below the specific challenges to Dr. Schneeweiss' opinions, but adopts and incorporates those portions of the Memorandum Ruling: Dr. Scott Delacroix, Urologic Oncologist (Rec. Doc. 3779) to the extent necessary to supplement the instant ruling.

The Defendants *do not challenge* Dr. Schneeweiss' *qualifications*, nor the *relevance* of his opinions, but focus their challenges entirely on the *reliability* of those opinions. Specifically, the Defendants argue that Dr. Schneeweiss' conclusions are *not reliable* because he "failed to apply a generally accepted methodology in a reliable and consistent manner . . . by predicating

his opinion on an inadequate factual basis and inconsistently applying recognized epidemiological principles when analyzing and weighing the clinical data he reviewed."[30] The Defendants' original arguments contained in their Memorandum are directed exclusively to challenging Dr. Schneeweiss' application of four of the Bradford Hill criteria, consistency of studies; strength of the association between pioglitazone and bladder cancer; a temporal association between exposure to pioglitazone and bladder cancer; and specificity of the association between pioglitazone and bladder cancer. Those will be addressed first; thereafter, this Court will address *the entirely new* arguments not asserted by the Defendants in their Response, but only now in their "Reply" Brief.

1. Original Memorandum: Application of the Bradford Hill Criteria.

The instant motion and original argument present a dispute which, primarily, focuses upon and is grounded within, the scientific discipline of epidemiology, which is the study of whether there is a *causal link* between harm and a potentially harm-causing agent. Consequently, this Court looks to the Reference Manual on Scientific Evidence for guidance and illumination.[31] Specifically, the Manual notes epidemiology does *not*, in fact, *establish causation as a scientific fact*, rather it presents *processes and analysis of/to amass and address data for epidemiologists to consider, analyze, evaluate, and from which to draw conclusions, based upon their judgment*.[32] Practitioners in this field agree that, in order to exercise their best judgment, epidemiologists should consider nine factors identified by Sir Austin Bradford Hill (a British physician) in 1965:

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[30] Memorandum, at 1.

[31] REFERENCE MANUAL ON SCIENTIFIC EVIDENCE (3d ed. 2011), hereinafter referred to as the "Manual."

[32] *See* Id., at 598.

- ***Temporal Relationship.*** The requirement that consequences occur after exposure to the harm-causing agent and not before.

- ***Strength of the Association.*** The relative risk that the agent will cause the consequence being studied.

- ***Dose-Response Relationship.*** Although not absolutely necessary, the existence of a dose-response relationship is a strong indication that the agent is causing the effect.

- ***Replication of the Findings.*** The more often the results have been replicated, the stronger the results are deemed to be.

- ***Biological Plausibility.*** Whether the current theory is consistent with existing knowledge.

- ***Consideration of Alternative Explanations.*** An epidemiologist who reaches one conclusion and refuses to consider any others has found a weak association, at best.

- ***Cessation of Exposure.*** If the reverse dose-response relationship also exists, *i.e.*, the cessation of exposure results in reduction in the incidents of the effect, then the causal relationship is very strong.

- ***Specificity of the Association.*** Non-scientific knowledge can sometimes be relevant to the epidemiological search for data on causation.

a. *Consistency.*

This Court previously has noted the very important role the Bradford Hill criteria play for a court determining the reliability of epidemiological conclusions as to causation. One of the criteria looks to the question of consistency: has the association between exposure to the pharmaceutical and the alleged injury caused by that exposure been observed by different persons in different places, under different circumstances, and at different times? Both the parties, and this Court, are in agreement that studies which have been replicated are more reliable and trustworthy than those that have not. The Defendants argue that the consistency requirement is not met here and, in the absence of demonstrated consistency, Dr. Schneeweiss' opinions are unreliable. The Defendants make several points in their brief:

- ***Unsupported Challenges.*** First this Court notes the Defendants make several arguments, or assertions of fact, which they, once again, do not support by reference to any evidence in the record, nor by any citation. For instance, the Defendants claim

that Dr. Schneeweiss "admittedly" did not consider all available evidence, but point to no evidence of such an admission.[33] In the absence of any such evidence, this Court can neither credit the assertion nor consider it as evidence of unreliability. As another example, the Defendants claim that Dr. Schneeweiss ignored inconsistency in animal laboratory studies.[34] Once again, these statements are not accompanied by any reference to evidence in the record, to the Schneeweiss Report, nor to any other demonstration that Dr. Schneeweiss actively ignored inconsistent animal studies, particularly in the face of factual evidence Dr. Schneeweiss considered, but did not embrace, possible studies which could be argued in contradiction to those embraced. Again, Defendants are cautioned, failure to embrace is not ignoring the existence of, if considered and distinguished – even if Defendants should disagree with the analysis used. In the absence of evidence supporting these statements, this Court cannot determine whether the Defendants' objections have any validity. The objection is, therefore, overruled.

- ***Defendants' Omnibus Exhibit G-1.*** The Defendants reviewed Dr. Schneeweiss' report and extracted information concerning 18 studies considered by Dr. Schneeweiss in the Schneeweiss Report, and put the information into a chart discussing overall results and attached it as their Exhibit G-1. The Defendants claim that the chart demonstrates Dr. Schneeweiss failed to consider all 18 of the studies in formulating his opinion. This Court is at a loss to understand this argument in light of the fact *the information on the chart was obtained from Dr. Schneeweiss' report.* Moreover, this Court's review of Dr. Schneeweiss' report demonstrates that it contains 28 pages of discussion of "the pioglitazone literature regarding bladder cancer," including each one of the studies listed by the Defendants in Exhibit G-1. These discussions identify the type of studies involved, the results shown, and the reliability or trustworthiness of the studies, their results, and Dr. Schneeweiss' use, or decision *not* to use, those studies. The Defendants clearly *do not agree* with Dr. Schneeweiss' *analysis* nor his *conclusions* about the persuasiveness of all 18 studies; however, it is equally clear that **he has not failed to consider the 18 studies identified in Exhibit G-1 and their findings**. This Court finds the Defendants' argument based on Exhibit G-1 unpersuasive, if not specious. Again, disagreement with is not ignoring of.

- ***Alleged Cherry-Picking.*** The Defendants allege that Dr. Schneeweiss "cherry picks" the data on which he relies, credits the minority of studies showing an increased risk associated with pioglitazone, and discredits the studies that find no significant association "by asserting that they were poorly conducted."[35] Defendants argue Dr. Schneeweiss' decisions to accept or reject studies amount to "cherry picking." This

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[33] Memorandum, at 4.

[34] Memorandum, at 4-5. (Dr. Schneeweiss "ignores the inconsistency in animal laboratory studies," "ignores the negative studies in other species," and "never even mentions the Actos® pre-clinical studies in monkeys, dogs, and mice that did *not* find an increased risk of bladder cancer, even though he agrees but it's important to consider animal experiments in determining potential causes of bladder cancer.")

[35] Memorandum, at 4.

Court disagrees, an expert can and does exercise his or her judgment and if he or she gives reasons for that decision and full explanation for those choices, disagreement with those choices becomes a matter for the trier of fact. The Defendants have provided this Court with no explanation for how or why Dr. Schneeweiss' methodology is incorrect, nor any reason to find that *his conclusions* about the trustworthiness of various studies are incorrect. In the absence of any basis for finding that Dr. Schneeweiss either abandoned correct scientific methodology of review, when on its face, the methodology is that used by experts within a given field when relying on underlying scientific studies and publications, or reached conclusions that are so patently wrong as to fail the gatekeeping inquiry, the Defendants' argument is unpersuasive.

- ***Irrelevant Studies.*** The Defendants allege Dr. Schneeweiss *ignores* laboratory studies finding that Actos® does not damage DNA.[36] As far as this Court can determine, this statement might or might not be correct. However, alleged DNA damage does not appear to play a role in the Plaintiffs' theory of general causation, therefore, this observation does not appear to be relevant to this Court's determination as to the admissibility or reliability of Dr. Schneeweiss' actual scientific opinion and anticipated testimony on the scientific theory that is actually being put forth by Defendants. Thus, Defendants' argument is unpersuasive.

- ***Actos® Might Show Cancer Benefits.*** The Defendants argue Dr. Schneeweiss *ignored* findings that Actos® might have anti-cancer properties in a variety of organ tissues – including bladder cells.[37] In support of this statement, the Defendants include citations to three scientific studies they allege Dr. Schneeweiss failed to consider. The Plaintiffs have not responded to this argument in any way, so the assertion is undisputed. However, the Defendants provide this Court with no explanation of those studies' findings, nor how those findings might actually impact Dr. Schneeweiss' opinions, nor what role those studies should have played in Dr. Schneeweiss' conclusions, nor do the Defendants provide this Court with any other way to evaluate the significance of the fact that Dr. Schneeweiss might not have considered these three studies. Consequently, Defendants' argument is wholly unpersuasive as they fail to demonstrate any significance of the unconsidered studies and, at best, raise a matter for cross-examination.

As noted above, this Court is guided by the Bradford Hill criterion of consistency, which asks, among other questions, whether the results of a study have been replicated. Dr. Schneeweiss' opinion is primarily founded upon one randomized controlled trial conducted by Takeda, as well as a meta-analysis of randomized trials, also conducted by Takeda. Dr.

[36] Memorandum, at 5.

[37] Memorandum, at 5.

Schneeweiss opines both studies demonstrate a significantly increased *risk* of bladder cancer with exposure to pioglitazone. Dr. Schneeweiss, also, considered one non-randomized study he considers to be of higher evidentiary value that he opines, also, concluded there exists a higher risk of bladder cancer for individuals who have been exposed to pioglitazone. Thus, Dr. Schneeweiss' report demonstrates an argument for *replication of his conclusions* at differing times, differing places, and under differing circumstances. The Defendants' narrow reading, and perhaps misunderstanding or misapplication of the consistency requirement, in the face of the actual opinion offered is somewhat disconcerting. However, Dr. Schneeweiss's *conclusion* is based upon multiple studies conducted in differing contexts, at differing locations and under differing circumstances, thus, granting the protection of replication. Dr. Schneeweiss conducted a review of multiple otherwise reliable studies in order to reach his conclusions. Within that review exist multiple studies, conducted at differing times, differing places and under differing circumstances. The fact that Dr. Schneeweiss does not put forth one laboratory study which he conducted, rather, reached a conclusion after review of laboratory studies conducted by others, an accepted methodology within his area of expertise, – is a distinction all parties would be well to keep in mind. Whether this methodology for reaching a given conclusion or opinion is *desirable* or *ideal* is not the *legal issue* before this Court at this juncture. Rather, whether Dr. Schneeweiss' use of the accepted methodology of reviewing otherwise sound evidence, data, studies and publications and reaching a conclusion and the formulating an opinion was properly applied by Dr. Schneeweiss is the inquiry at hand, and this Court finds Defendants have failed to meet the Plaintiffs' *prima facie* showing by demonstrating that it was not. Any disagreements, weaknesses, or flaws, are fodder for vigorous cross-examination and the evaluation of the trier of fact.

Of course, in theory, the more often a study's results or the basis for a conclusions is replicated, the more reliable those results or conclusions are. The discipline of epidemiology suggests that replication is quite significant when looking toward a general consensus on a possible or probable causal relationship between agent and effect; however, as the authors of the Manual recognize, reliability does not necessarily turn on whether a study has been replicated by the time trial commences, *nor necessarily does the legal standard at play*.[38]

Dr. Schneeweiss' report contains, in addition to the three studies discussed above, discussions of 16 additional epidemiological studies. Some of these studies have findings that agree with Dr. Schneeweiss' conclusions, and some of these studies reach conclusions that disagree with Dr. Schneeweiss' opinions. However, Dr. Schneeweiss reviews, addresses and considers each of the studies. Additionally, this Court notes the mere existence of conflicting, contradictory results does not, in and of itself, render any expert and here, Dr. Schneeweiss' opinions necessarily unreliable scientifically or inadmissible legally. One-hundred percent agreement is so rare within human endeavors, whether in matters great or small, as to be almost unheard of, and certainly legal admissibility does not impose such an unrealistic requirement upon the scientific method. Rather, *admissibility* within the law, our inquiry here, rests upon scientific *reliability* which, also, does not embrace the stringent standard argued by Defendants. An expert who finds studies that, arguably, are inconsistent with other studies in his or her opinion, ideally should consider those inconsistent studies in preparing his or her opinions and present his or her reasons for his or her conclusions reached. Dr. Schneeweiss has conducted

[38] "It is important that a study be replicated in different populations and by different investigators before a causal relationship is accepted by epidemiologists and other scientists." MANUAL, at 604. However, "[t]his may not be the legal standard . . .." Id., at n.163 (*citing* Smith v. Wyeth-Ayerst Labs Co., 278 F.Supp.2d 684, 710, n.55 (W.D.N.C. 2003) (observing that replication is difficult to establish when there is only one study that has been performed at the time of trial).

such a review and analysis in this case. Consistency and agreement among studies reviewed is certainly desirable, but differing results and opinions are not disqualifying.

Dr. Schneeweiss' report contains ample evidence that he considered the entire scientific picture before him, considered both supporting and, arguably, inconsistent evidence, and developed opinions that he explains by way of the evidence he finds persuasive, and explains the evidence he finds unpersuasive, and gives his reasons why. Again, this Court notes that, once again, there are two distinct inquiries afoot, with distinct and differing underlying processes, goals, and rationales at play, which are being conflated by the Defendants' arguments. One involves the formulation of opinion, the other the examination of that opinion. One plays a significant role in science and, the other in law, both might be strong fodder for cross-examination in determining the other – however, the two goals are not one and the same – a distinction not, it would seem, fully appreciated within the Defendants' arguments. An expert is free to rely upon those studies he or she believes to be significant and to distinguish others he or she does not; he or she is, however, not permitted to *ignore* accepted scientific and/or medical evidence and merely opine based upon his or her underlying education or training.[39]

The Defendants, also, assert Dr. Schneeweiss "cherry picks" studies in order to formulate his opinions.[40] Dr. Schneeweiss might not give the answer the Defendants desire, but that is an expert's prerogative. Dr. Schneeweiss might not embrace the studies the Defendants champion, but he explains that choice. If such an explained choice is to be considered "cherry-picking," as Defendants argue, then Defendants' experts would likely be equally guilty, as well. These and other equally problematic arguments fail to demonstrate such inconsistency as to render Dr. Schneeweiss' opinions unreliable. Consequently, this Court finds Defendants' arguments

[39] Brown, 705 F.3d at 535.

[40] Memorandum, at 5.

concerning the alleged lack of consistency of studies supporting Dr. Schneeweiss' conclusions to be unpersuasive.

b. *Strength of Association.*

The Defendants challenge the strength of the association that Dr. Schneeweiss found between exposure to pioglitazone and bladder cancer. As before, the Defendants assert a number of challenges:

- ***Causation Conclusions.*** The Defendants claim that "[n]ot a single epidemiological study cited by Dr. Schneeweiss says Actos® *causes* bladder cancer."[41] As this Court has previously noted, epidemiological studies are designed to gather data for use by epidemiologists *in determining possible causal relationships*. Such studies do not, and cannot, present conclusions as to causation. Therefore, the fact that none of the epidemiological studies cited by Dr. Schneeweiss reaches such a conclusion is of no moment to this Court's analysis of the reliability of Dr. Schneeweiss' opinions. Defendants' argument is unpersuasive.

- ***Brigham & Women's Hospital.*** The Defendants argue that Dr. Schneeweiss' opinions are unreliable because one of his employers, Brigham & Women's Hospital, does not claim that Actos® is a cause of bladder cancer.[42] The apparently-undisputed fact that Brigham & Women's Hospital has reached no conclusion that Actos® is a cause of bladder cancer does not enlighten this Court as to the inquiry at hand. This Court has no information with which to determine whether the hospital disagrees or agrees with Dr. Schneeweiss' conclusions; whether the hospital has considered or not considered the same evidence that Dr. Schneeweiss discusses in his report; nor whether the Defendants have or have not released Dr. Schneeweiss from his confidentiality agreement to allow him to engage in a discussion with his employer about the side effects of Actos®. Nor, in candid response, can this Court glean either from Defendants' argument or the law, why this Court would find such information relevant or in any fashion persuasive *to the inquiry at hand*. Perhaps a basis for flashy cross-examination, such information, however, does not seem at all relevant to the Daubert inquiry and challenge before this Court, nor does Defendants' argument enlighten the Court as to the legal inquiry at hand. This Court does not see that the stance of Brigham & Women's Hospital on Actos® as a cause of bladder cancer is of any relevance to the determination of the admissibility of Dr. Schneeweiss' opinions. Defendants' argument is unpersuasive.

- ***Relative Risk Values.*** The Defendants state that, "The studies on which Schneeweiss relies for his general causation opinion include relative risks that fall close to, and

[41] Memorandum, at 6 (emphasis in original).

[42] Memorandum, at 6.

even below, the 1.4 mark,"[43] and cites to a discussion of the "meta-analyses of observational studies," a subset of "non-randomized studies of moderate evidentiary value and with some identifiable biases" that Dr. Schneeweiss considered in forming his opinion. Had Dr. Schneeweiss relied solely on studies yielding a relative risk of 1.4 or lower, this Court might be inclined to question whether Dr. Schneeweiss' review, investigation, and conclusions were reliable. However, the Schneeweiss Report demonstrates his conclusion as to the strength of the association between pioglitazone exposure and bladder cancer is based upon Takeda's meta-analysis of randomized trials, which demonstrates a 2.64 relative risk, together with the meta-analysis of the higher-quality observational studies with a relative risk of 1.38. According to Dr. Schneeweiss' testimony, the latter meta-analysis has limited usefulness, but it, nonetheless, supports the conclusion that an association between the exposure and the disease exists. This Court finds Dr. Schneeweiss' reliance on a meta-analysis with a "modest" relative risk does not, under these circumstances, necessarily render his opinions unreliable, rather presents rich fodder for vigorous cross-examination. Defendants' argument is unpersuasive.

- ***Establishing Causation.*** The Defendants attempt to demonstrate that Dr. Schneeweiss' opinions are unreliable by claiming that, "Dr. Schneeweiss is not always consistent in his opinion that a 1.2 to 1.4 relative risk establishes causation."[44] However, this Court has closely reviewed Dr. Schneeweiss' report and finds that he has not opined that a study demonstrating a 1.2 to 1.4 relative risk "establishes causation" as Defendants' argument implies. The record does not contain any indication that Dr. Schneeweiss would have reached any of his opinions about causation had he reviewed studies that reflected *only* a relative risk of 1.2 to 1.4. As noted above, Dr. Schneeweiss relied heavily on the randomized clinical trials and meta-analysis conducted by Takeda in concluding there is a strong association between pioglitazone exposure and bladder cancer. Moreover, the Defendants cite this Court to the Azoulay study[45] for the proposition that a relative risk of 1.2 to 1.4 is a "modest increased risk." While the authors of the Azoulay study do agree that a 1.2 to 1.4 relative risk is "modest," their own conclusions were that: "Overall, ever [sic] use of pioglitazone was associated with an increased rate of bladder cancer (rate ratio 1.83, 95% confidence interval 1.10 to 3.05). The rate increased as a function of duration of use, with the highest rate observed in patients exposed for more than 24 months (1.99, 1.14 to 3.45) and in those with a cumulative dosage of greater than 28,000 mg (2.54, 1.05 to 6.14)." In other words, the Azoulay study did not find a "modest" 1.4 relative risk, but a risk that varies from 1.99 to 2.54 and averages 1.83, a value that, it would seem, represents a near-doubling of risk. The Defendants have failed to establish that Dr. Schneeweiss misused or misapplied relative risk ratios, and have, instead, directed this Court's attention to evidence that would seem to reinforce

[43] Memorandum, at 7.

[44] Memorandum, at 7.

[45] Defendants' Omnibus Exhibit F3.

the reliability of Dr. Schneeweiss' conclusions. Defendants' argument is unpersuasive.

This Court notes that Dr. Schneeweiss' discussion of the strength of the association he finds between pioglitazone exposure and bladder cancer is found at page 50 of his report. At no time during the Defendants' briefing have they addressed the actual bases identified by Dr. Schneeweiss as to the foundation for his determination that the association between exposure to pioglitazone and bladder cancer is strong. However, this Court *has* reviewed Dr. Schneeweiss' explanation for his conclusions that the association between pioglitazone exposure and bladder cancer is a strong one. On its face, it appears to be reasoned and supported, and to result from the considered analysis required by the scientific method of responsible review. None of the Defendants' arguments have demonstrated Dr. Schneeweiss' methods or conclusions are unreliable, nor that they demonstrate so weak a causal association as to be unreliable. That is not to say, of course, that this Court *agrees or disagrees with Dr. Schneeweiss' conclusions* – it has no such opinion – as *that is not the inquiry* before the Court today. Reliability is not necessarily accuracy, just as disagreement with is not ignoring of. This Court finds the Bradford Hill criterion of strength of association is met by Dr. Schneeweiss' analysis and weighs in favor of the reliability of his opinions.

c. *Temporal Association.*

The Bradford Hill criterion of temporal association between exposure and effect has been deemed to be important to an epidemiological conclusion as to causation. The Defendants challenge Dr. Schneeweiss' reliance on studies -- the Defendants have not actually identified *which* studies they challenge in this section, but this Court *assumes* they intend to challenge the same studies as were challenged in earlier motions, specifically, the randomized clinical trials - they argue do not show a causal association between pioglitazone exposure and bladder cancer.

The particular challenge mounted by the Defendants relies on a latency period for bladder cancer that "requires years of growth from a single cell to a diagnosable tumor."[46]

The Defendants argue here, as they have argued elsewhere, that it would have been *impossible* for any instance of bladder cancer discovered during the first year of the randomized clinical trials of pioglitazone to have been caused by exposure to Actos. This Court's ruling on that subject is found at Rec. Doc. 3771 (Memorandum Ruling: Development of Bladder Cancer Within One Year of Exposure) and is incorporated and adopted herein. The instant motion references, implicitly or otherwise, issues that this Court has already ruled on, and this Court finds the Defendants' arguments in the instant motion have not persuaded this Court to reconsider its earlier conclusions. Again, the analysis, rationale, and conclusions reflected in Rec. Doc. 3771 are adopted and incorporated herein as supporting this Court's findings, conclusions and ruling made herein. This Court notes, however, certain of Defendants' arguments are slightly different in the instant motion, consequently, this Court will address those new arguments directly.

The Defendants' temporal association argument now made, relies heavily on general statements *which, again, are not supported by citation to the Schneeweiss Report, nor to Dr. Schneeweiss' deposition testimony*. For instance, Defendants' temporal association argument contains no reference to any particular study under challenge.[47] If for no other reason, the

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[46] Memorandum, at 8.

[47] For instance, the Defendants' Memorandum includes the following statements: "However, [Dr. Schneeweiss] is unable to reliably account for the likelihood that bladder cancer existed in some participants of the studies on which he relies well before they ever took Actos." (page 8) The Defendants do not identify the "studies on which he relies." Similarly, the "Actos studies on which [Dr. Schneeweiss] relied did not specifically screen for undiagnosed bladder cancer, and Dr. Schneeweiss concedes that he does not know what screening for bladder cancer was performed prior to commencement of the studies." (page 8) Again, the Defendants have not identified the studies under challenge. However, this Court assumes the study to be the PROactive clinical trial. Later, "[Dr. Schneeweiss] cannot say with any assurance that the bladder cancers in the studies began *after* the patients in the studies began using Actos." (page 8) Once again, no identification of which studies are being discussed. Finally, "[a]bsent some basis for concluding that the patients in the studies on which he relies were exposed to Actos before

Defendants' challenge should be overruled for the abject failure to provide this Court with sufficient information to conduct a rational, considered analysis of the challenge. However, as noted above, this Court assumes the Defendants' challenge is to the same randomized clinical trials challenged in other of Defendants' Daubert motions; the most significant of these clinical trials being the PROactive study that was conducted by Takeda.

As this Court has noted previously, it is undisputed the PROactive clinical trial was well-designed, and that its execution is not under challenge. Nonetheless, the Defendants argue the Plaintiffs' experts' conclusions, which are based upon consideration of data including those instances of bladder cancer that developed within one year of exposure to pioglitazone, are not reliable because the experts cannot *prove* that the bladder cancers occurring during the first year of the PROactive study were, in fact, caused by Actos®. As discussed in part in earlier rulings on this subject, this argument suggests a misapprehension of the nature of epidemiological studies and the legal requirement at hand, which this Court finds perplexing given the sophistication of the Defendants' counsel. Within the discipline of epidemiology, it is neither necessary nor appropriate, nor is it likely, possible for an epidemiologist to determine the *actual cause* of any given subject's illness, particularly *before* using that data to determine whether any *possible* association might exist. An epidemiological study is conducted *for the purpose* of obtaining data with which to evaluate *whether* a causal association *likely exists or likely does not exist*. Thus, epidemiological studies are *designed to generate statistical data* in support of *the scientific effort to determine* what, if anything, that data might reveal about a possible causative relationship or association, here, between Actos® and any side effects that might come to light during the study. It would not be appropriate to use, nor do Plaintiffs' experts, nor Dr.

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they developed bladder cancer, Dr. Schneeweiss cannot reliably conclude that there is causation based on those studies." (page 9) Again, merely a generic reference is made.

Schneeweiss in particular, attempt to use, the Defendants' epidemiological study to attempt to make findings as to *specific causation in a particular study subject,* nor is it appropriate to argue *one must know the desired result of data found within a study before engaging in the very study* designed to determine *if there is a given association at play.* Requiring a scientist *to prove causation* in order to use data in an epidemiological inquiry, to determine if there is a causal relationship, it would seem, would render the exercise of conducting an epidemiological study entirely meaningless. Furthermore, the same argument made by Defendants as to those instances of cancer appearing within one year, would seem to apply to those appearing after one year, and within any epidemiological study if taken in the very broad and absolute manner argued by Defendants. This Court finds Defendants' argument on this point wholly unpersuasive.

d. Specificity.

Defendants' argument as to specificity, it would seem, centers upon a confusing at best, and, quite perplexing understanding and application of the Hill criterion, and one argued to this Court in previous motions. As previously noted, the specificity requirement within the Hill criteria does not limit causation findings to only those instances where a particular agent is the sole, and only possible, cause of a signature disease.[48] Rather, the specificity requirement calls for a strong skepticism when *one* agent is alleged to cause *many different* types of disease.[49] In this case, the Plaintiffs' argument alleges that pioglitazone causes bladder cancer and nothing more. Therefore, the Plaintiffs do not seem to have created the doubt as to the specificity of the causal link asserted and argued by the Defendants. The Defendants' argument as to this point is wholly without merit.

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[48] *See* Memorandum, at 9 ("Dr. Schneeweiss concedes there is no evidence to suggest that the type of bladder cancer that occurs in Actos® users is in any way unique from bladder cancers that occurs [*sic*] in non-Actos® users.").

[49] MANUAL, at 605-06.

2. Reply Memorandum: Basic Epidemiological Concepts And The Usefulness of Studies

The Defendants' Reply brief, again and also, reiterates several arguments made in their original Memorandum; this Court will not revisit those discussions here, but refers the parties to earlier discussions of the Bradford Hill criteria and the application of those criteria by Dr. Schneeweiss. However, in their Reply Brief, the Defendants did introduce two entirely new arguments: (a) Dr. Schneeweiss' allegedly erroneous application of basic, longstanding epidemiological concepts; and (b) the complete unreliability of three studies identified by Dr. Schneeweiss in his Report. Notwithstanding this Court's concern that Defendants have introduced virgin arguments within their Reply brief and thereby putting Plaintiffs at unfair disadvantage, as this Court finds those arguments unpersuasive, this Court will address those new arguments and will address them separately.

a. The Application Of Basic Epidemiological Concepts

Two fundamental concepts used by epidemiologists and statisticians to maximize the likelihood that results are trustworthy are p-values, the mechanism for determining "statistical significance," and confidence intervals; each of these mechanisms measures a different aspect of the trustworthiness of a statistical analysis. There is some controversy among epidemiologists and biostatisticians as to the relative usefulness of these two measures of trustworthiness, and disputes exist as to whether to trust p-values as much as one would value confidence interval calculations.[50]

The Defendants have demonstrated Dr. Schneeweiss is an epidemiologist who questions the value of statistical significance findings and who does not place his trust in general rules

[50] MANUAL, at 578-79.

about confidence intervals above his own informed analysis of the statistical evidence.[51] Dr. Schneeweiss is free, of course, to have his own opinions, to discuss those opinions at length during his deposition, and to agree with whichever side of the ongoing scientific debate best reflects his understanding of scientific trustworthiness and validity. However, this Court sits in the Fifth Circuit and, therefore, this Court's analysis is bound by the doctrine of *stare decisis* and the Fifth Circuit's policy determinations on the admissibility of statistical and epidemiological evidence. The Fifth Circuit long ago made it clear that experts who fail to comply with the prevailing statistical and epidemiological principles will not be permitted to testify because their conclusions are deemed unreliable.[52] As a result, Dr. Schneeweiss' statistical analyses and causal conclusions will be held to those standards the Fifth Circuit has adopted.

This Court has closely reviewed Dr. Schneeweiss' Report and finds there is no indication Dr. Schneeweiss has abandoned either statistical significance or confidence intervals as ways of evaluating the value and trustworthiness of epidemiological studies and the conclusions that they reach. The Defendants' Reply brief, aside from showing that Dr. Schneeweiss disagrees with the Fifth Circuit on the importance of p-values and the proper use of confidence intervals, does not challenge Dr. Schneeweiss' reliance on the studies identified in his Report, but limits the Defendants' challenge to only four specific studies (the Lewis study, the Chang study, the Tseng study, and the Wei study).[53] Specifically, the Defendants claim those studies have confidence intervals which demonstrate untrustworthiness, argue that those studies should not have been used by Dr. Schneeweiss, and, therefore, Dr. Schneeweiss' reliance on those studies renders Dr.

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[51] *See* the Schneeweiss Report, at 28; Defendants' Omnibus Exhibit B9 (Schneeweiss Deposition), at 165, 228-229.

[52] *See, e.g.*, Brock v. Merrell Dow Pharmaceuticals, Inc., 874 F.2d 307, 312 (5th Cir. 1989). *But see* discussion of the controversy, MANUAL, at 578-79 n.85.

[53] Reply, at 3.

Schneeweiss' conclusions untrustworthy. The Schneeweiss Report reveals *three of the four studies argued by the Defendants* ***were rejected*** *by Dr. Schneeweiss and played no role in his conclusions*,[54] and *the fourth study was found by Dr. Schneeweiss to be "clearly biased towards the null"* (meaning, in layman's terms, that the design of the study biased it toward a finding of no association), but in his opinion shows a, nonetheless, *dose-response* relationship between pioglitazone and bladder cancer.[55] A close review of Dr. Schneeweiss' testing, therefore, reveals he did not rely on the fourth study (the Lewis study) in the way the Defendants' argument suggests; and rejected the other three studies argued by Defendants. Consequently, as Dr. Schneeweiss rejected three of the four studies Defendants base this challenge upon and found the fourth "clearly biased toward the null," Defendants' argument, it would seem, is again the setting up of a straw man, only to ask the Court to strike him down.

Therefore, looking to Dr. Schneeweiss' *actual analysis and conclusions about pioglitazone*, rather than to his possible philosophical differences with the scientific community, this Court concludes the Defendants have not demonstrated Dr. Schneeweiss failed to apply or misapplied the basic epidemiological and statistical concepts that reflect the Fifth Circuit-approved standard scientific methodology in his field. To the contrary, three of the four studies challenged by the Defendants as "worthless" were, also, rejected by Dr. Schneeweiss, and the fourth study was identified as clearly biased toward the "null" – and, therefore, addressed and severely limited by Dr. Schneeweiss for precisely the reasons the Defendants challenge its value. In the absence of any evidence Dr. Schneeweiss applied the wrong standards when he conducted his analysis, or that he allowed his personal preference for the more flexible analytical approach

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[54] *See* the Schneeweiss Report, at 45-46 (where Dr. Schneeweiss rejects the Chang, Tseng, and Wei studies as flawed and declaring that they have not contributed to his conclusions).

[55] Id. at 42-43.

to govern his actual conclusions made or to lead him to misapply epidemiological principles during the development of his opinions in this matter, this Court finds that his application of basic epidemiological methods is not unreliable for the reasons Defendants argue. Again, had Dr. Schneeweiss actually employed the disapproved standards, Defendants argument would be persuasive, however, Defendants present no evidence he did so. Rather, the evidence is to the contrary when viewed within the context of the four studies argued by Defendants to support their argument. The Defendants' argument is unpersuasive.

b. The Usefulness of the Three Studies

The Defendants' final challenge to Dr. Schneeweiss' opinions focuses on three studies the Defendants' argue are unreliable. Each is addressed separately.

The Neumann Study. The Defendants challenge the Neumann Study: "Plaintiffs omit that the study's statistically significant increased risk appeared only after the study authors omitted without explanation almost a quarter million of the study participants over a certain age."[56] This argument is unpersuasive for several reasons.

First, the argument is unsupported. The Defendants do not in any way explain their assertion that the Neumann Study authors "omitted without explanation" almost a quarter of a million study participants. This Court has reviewed the published study itself and found no evidence of such an omission. Without knowing the source of the Defendants' assertion, this Court cannot evaluate the argument rationally and must overrule the objection on that ground alone. Again, unsupported factual assertions serve neither the Defendants nor their cause.

Second, Dr. Schneeweiss included in his Report a three-paragraph discussion of the Neumann authors' exclusion of individuals aged 80 and over from their study.[57] *If,* however, this

[56] Reply, at 9.

[57] *See* the Schneeweiss Report, at 36.

Court were *to assume* these are the individuals Defendants argue whose omission from the study was made allegedly "without explanation" (as this Court suspects, but as the Defendants have not actually articulated), then it is inaccurate to argue the Plaintiffs have failed to address the Defendants' concern, because full explanation appears in the Schneeweiss report itself. If these individuals are not the ones referred to by the Defendants in their Memorandum, then this Court, again, cautions Defendants against bald factual assertions unsupported by citation, either legal or factual. Whether the "exclusion" as explained by Dr. Schneeweiss was scientifically valid and does or does not create a statically relevant anomaly, remains a question for cross-examination and not one for the gatekeeper.

Finally, the Defendants assert the Neumann study authors "omitted without explanation almost a quarter million of the study participants *over a certain age*," (emphasis added) implying the exclusion was effected for the purpose of skewing the results of the study. Once again, this Court assumes the Defendants are referring to the Neumann authors' decision to limit their cohort to individuals aged 40 – 79. Neither the Defendants nor the Court located an explanation for this decision in the published Neumann study. However, Dr. Schneeweiss' Report contains information about the Neumann authors' choice and is available for vigorous cross-examination.[58]

Specifically, Dr. Schneeweiss indicates the French reporting system, which was the source of data on which the Neumann authors conducted their analysis, only records data for those individuals who actually receive treatment for bladder cancer. Because individuals in France over the age of 80 receive treatment at far lower rates than do those who are under the age of 80 when diagnosed, the French database, therefore, does not include complete information on the group of individuals who were 80 or over when diagnosed. For this reason, this Court

[58] The Schneeweiss Report, at 36.

assumes, if this Court is reading Dr. Schneeweiss' report correctly, the authors of the Neumann study only included individuals aged 40 – 79 because that was the only cohort for which they had full data. Thus – and contrary to the Defendants' argument – an explanation not only exists, but more importantly was discussed and given by Dr. Schneeweiss.[59] Whether the omission was a scientifically significant one and whether made for a scientifically valid reason, again, seems quite reminiscent of Plaintiffs' argument as to the PROactive study and omission of those instances of bladder cancer exhibiting within one year – and, again, this Court finds the question is not one for the gatekeeper, but for the trier of fact.

The Defendants have neither acknowledged Dr. Schneeweiss' explanation, provided any counter-argument, nor distinguished their argument here from the similarity of the argument made as to the PROactive study. Their silence on the point and lack of evidence and persuasive argument leads this Court to conclude that there is no merit to their objection.

The Bosetti Study. The Defendants assert the authors of the Bosetti study made two statements that render their study so unreliable that Dr. Schneeweiss should not have used it in his analysis. First, the Bosetti study authors declare that they know of "no clear biological mechanism that can explain the apparent increase in bladder cancer risk in pioglitazone users."[60] This statement implies support for the existence of an outside mechanism and thus, the argued increased risk and association with the use of pioglitazone. Again, the authors' statement that they know of no such biological association in and of itself and on its face and without biological evidence to the contrary, does not render the study so unreliable as to undermine Dr. Schneeweiss's opinion for relying on the study. Equally important, the statement alone does not

[59] Dr. Schneeweiss does not identify his source for this discussion, so this Court cannot evaluate the actual reasonableness of either the explanation or the decision to limit the cohort in this fashion. This Court has described Dr. Schneeweiss' decisions only to demonstrate that the Defendants' assertion is incorrect that no explanation exists for the authors' decision.

[60] Reply, at 9.

undermine the reliability *of the data derived through the study*. Again, Defendants do not present biological evidence to disprove the authors' statement, nor do Defendants present evidence or persuasive argument as to the actual data created by the Study. The fact Defendants take umbrage with one of the author's statements made, is, again a matter better addressed on cross-examination when exploring the multiple bases of Dr. Schneeweiss's opinion.

Second, the Bossetti authors indicate they found an increased risk profile for exposure to pioglitazone and that the risk profile shows a dose-response relationship,[61] but found that the relationship was "modest," and they could not conclude that the relationship was causal in nature.[62] It certainly appears to be true, as the Defendants suggest, that the Bosetti study alone does not, and cannot, support a finding that pioglitazone *causes* bladder cancer, but it is also very clear that Dr. Schneeweiss did not use the Bosetti study in that way. In fact, Dr. Schneeweiss appears to share the Defendants' skepticism about the Bossetti study, hence his determination that it is of "moderate evidentiary value with some identifiable biases".[63] The Schneeweiss Report indicates, however, that he, also, revised the Bosetti analysis by removing "low quality studies" and adding new, higher-quality studies before considering it at all.[64] Again, the dispute at hand is one better suited to cross-examination as to Dr. Schneeweiss – as it is his opinion being challenged.

The International Agency for Research on Cancer, Working Group Determination. The third study challenged by the Defendants as "unsupportive" of Dr. Schneeweiss' opinions is the Working Group Determination issued by the International Agency for Research on Cancer

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[61] *See* Defendants' Exhibit 2 to Reply Brief, at 5-6.

[62] Id. at 6.

[63] The Schneeweiss Report, at 35-40.

[64] Id. at 40.

("IARC").[65] The Defendants note that the IARC "was unable to consistently rule out confounding and bias related to disease severity and detection," and that the Working Group's conclusions were reached on "limited evidence."[66] Certainly, both of these elements of the IARC Determination should engender care in any epidemiologist seeking to rely upon that Determination as supporting evidence for an opinion. However, this Court has found no evidence – nor have the Defendants pointed to anything in the record suggesting – that Dr. Schneeweiss has failed to acknowledge the IARC Determination's inherent limitations or otherwise misapplied its conclusions.

The IARC Determination contains statements, opinions, conclusions, and caveats that are definitive, yet limited:

> Pioglitazone was assessed in an analysis of one large randomised controlled trial, four cohort studies, and three case-control studies. Ever-use of pioglitazone was associated with an increased risk of bladder cancer in all except for one case-control study from Taiwan, and across all study designs and geographical regions, with RRs ranging from 1.2 in the observational studies to almost 3 in the randomised controlled trial. Dose-response associations were assessed in five studies, three of which were high-quality population-based studies. Increased risks were reported with higher dosage or longer use in one case-control study and in one cohort study. However, the Working Group was unable to consistently rule out confounding and bias related to disease severity and detection. Notably, Pioglitazone induced an increased incidence of urinary bladder transitional cell carcinoma or papilloma in male rats in two individual gavage studies. Urolithiasis or peroxisome proliferator-activated receptor-mediated effects seemed to be the most likely mechanisms of carcinogenesis. Pioglitazone was classified as probably carcinogenic to humans (group 2A), on the basis of limited evidence in humans that it causes urinary bladder cancer, and sufficient evidence in experimental animals.[67]

This Court finds that as the IARC Determination provides limited support for the proposition that Pioglitazone can cause bladder cancer in humans, should Dr. Schneeweiss

[65] *See* Exhibit 3 to Reply Brief.

[66] Reply Brief, at 10.

[67] Defendants' Exhibit 3 to Reply Brief, at 807. (citations omitted)

choose to add this report to his support for his opinion, that is a choice he may make, albeit at his own possible peril, as, again, the study's noted weaknesses will again likely be rich fodder for cross-examination. However, as the Defendants have not addressed how Dr. Schneeweiss might have used the IARC Determination in his report - they addressed their argument solely to Dr. Schneeweiss' decision to address the Determination at all - this Court, again, finds the Defendants have not demonstrated that Dr. Schneeweiss either misapplied or otherwise relied in error on the IARC Determination in such a way as to fully undercut Dr. Schneeweiss' opinion. The Defendants' argument is unpersuasive.

III. EVIDENTIARY HEARING

The Defendants requested this Court agree to hear live testimony from the experts prior to ruling on the Daubert motions in this case. This Court carefully considered the Defendants' request. However, the decision of how to go about ruling on the instant motion is squarely within this Court's discretion.

> The trial court must have the same kind of latitude in deciding *how* to test an expert's reliability, and to decide whether and when special briefing or other proceedings are needed to investigate reliability, as it enjoys when it decides whether or not that expert's relevant testimony is reliable. Our opinion in Joiner makes clear that a court of appeals is to apply an abuse-of-discretion standard when it reviews a trial court's decision to admit or exclude expert testimony. That standard applies as much to the trial court's decisions about how to determine reliability as to its ultimate conclusion. Otherwise, the trial judge would lack the discretionary authority needed both to avoid unnecessary "reliability" proceedings in ordinary cases where the liability of an expert's methods is properly taken for granted, and to require appropriate proceedings in the less usual or more complex cases where cause for questioning the expert's reliability arises. Indeed, the Rules seek to avoid unjustifiable expense and delay as part of their search for truth and the just determination of proceedings.[68]

This Court reviewed the extensive briefing provided by both parties, as well as the large number of exhibits, including expert reports, depositions, and other documents, and concluded

[68] Kumho Tire, 526 U.S. at 152-53 (emphasis in original) (citations and quotations omitted).

the nature of the challenges presented and the arguments made did not illustrate a need for live testimony, which would not be likely to contribute to any greater understanding of the nature of the dispute than can be and has been found in a careful reading and analysis of the briefs and accompanying evidence and documentation. The request for an opportunity to present live testimony in an evidentiary hearing is DENIED.

CONCLUSION

For the foregoing reasons, the Defendants' Motion to Exclude Testimony of Plaintiffs' Expert, Sebastian Schneeweiss, M.D., S.M., S.C.D., F.A.C.E., F.C.P., F.I.S.P.E., shall be DENIED.

THUS DONE AND SIGNED this 7 day of January, 2014.

REBECCA F. DOHERTY
UNITED STATES DISTRICT JUDGE